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# The Prevalence, Incidence and Prognostic Value of the Brugada-Type Electrocardiogram

## A Population-Based Study of Four Decades

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**OBJECTIVES** We sought to demonstrate the prevalence, incidence and prognostic value of the Brugada-type electrocardiogram (ECG) in a general population.

**BACKGROUND** The Brugada syndrome is characterized by evidence of right bundle branch block and ST segment elevation in the right precordial leads, as well as sudden death caused by ventricular fibrillation. However, the natural history of the Brugada-type ECG remains unclear.

**METHODS** We investigated 4,788 subjects (1,956 men and 2,832 women) who were <50 years old in 1958 and had undergone biennial health examinations, including electrocardiography, through 1999. The Brugada-type ECG was defined as a terminal r′ wave in lead $V_1$ and ST segment elevation ≥0.1 mV in leads $V_1$ and $V_2$. Unexpected death was defined as sudden death or unexplained accidental death.

**RESULTS** There were a total of 32 Brugada-type ECG cases; the prevalence and incidence were 146.2 in 100,000 persons and 14.2 persons per 100,000 person-years, respectively. The incidence was nine times higher among men than women, and the average age at presentation was 45 ± 10.5 years. The Brugada-type ECG appeared intermittently in most cases and was found in 26% of subjects who died unexpectedly. Cox survival analysis revealed that mortality from unexpected death was significantly higher in subjects with a Brugada-type ECG than in control subjects ($p < 0.01$). Unexpected deaths were more frequent among subjects with the Brugada-type ECG who had a history of syncope ($p < 0.05$).

**CONCLUSIONS** The Brugada-type ECG is not a very rare condition in the adult Japanese population. Subjects with a Brugada-type ECG have an increased risk of unexpected death. (J Am Coll Cardiol 2001;38:765–70) © 2001 by the American College of Cardiology

Ventricular fibrillation (VF) without obvious cardiac pathology (i.e., idiopathic VF) accounts for 1% to 9% of survivors of out-of-hospital cardiac arrest (1). In 1992, Brugada and Brugada (2) reported eight patients with idiopathic VF, now known as Brugada syndrome, which is characterized by an electrocardiogram (ECG) showing evidence of right bundle branch block and ST segment elevation in the right precordial leads. This ECG pattern, also called the Brugada-type ECG, was once considered a probable normal variant (3). Since the Brugadas' report (2), however, attention has been directed to the relationship between the Brugada-type ECG and sudden death. Nevertheless, epidemiologic information on the Brugada-type ECG is scarce.

The present study, based on a 40-year follow-up of 4,788 subjects in Nagasaki, Japan, was carried out to investigate the natural history of the Brugada-type ECG, including its prevalence, incidence and long-term prognostic value in the general population.

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## METHODS

**General procedure.** A total of 7,564 subjects (3,374 men and 4,190 women) have received biennial examinations in Nagasaki since 1958, as part of a follow-up program of the Radiation Effects Research Foundation. A detailed description of the program has been published elsewhere (4,5). Of those subjects, we investigated 4,788 (1,956 men and 2,832 women) who were <50 years old in 1958. At each examination, the subjects were interviewed for symptoms, including chest pain or syncope. Physical examination was performed and blood pressure was measured with the subject in the sitting position. They underwent standard 12-lead electrocardiography and chest radiography. Data from 1958 to 1959 (the first examination) through 1998 to 1999 (the 21st examination) were analyzed in the present study.

**Definition of the Brugada-type ECG.** We characterized an ECG as the Brugada type if it showed the following: 1) a terminal r′ wave in lead $V_1$, characterizing right bundle branch block; 2) a convex curve or "coved"-type ST segment elevation ≥0.1 mV in lead $V_1$ or in leads $V_1$ and $V_2$; and 3) "saddle-shaped"-type ST segment elevation ≥0.1 mV in lead $V_2$ or $V_3$, or both (Fig. 1). An ECG was not characterized as the Brugada type either if the ST segment elevation in the right precordial leads showed the "saddle-shaped" type alone in leads $V_1$ to $V_3$ or if the ST segment

**Abbreviations and Acronyms**
ECG = electrocardiogram
VF = ventricular fibrillation

elevation was accompanied by reciprocal ST segment depression in opposite leads (6,7).

The time course of ST segment abnormalities was classified into one of two categories: 1) a persistent course showing permanent abnormalities; or 2) an intermittent course showing transient normalization of the ST segment pattern during follow-up (Fig. 2). In subjects with an intermittent course of ECG abnormalities, the onset of the Brugada-type ECG was defined as the first appearance of the ECG manifestation during follow-up.

The ECG records of all study subjects were reviewed by Dr. Matsuo, without reference to death certificate information. Drs. Hayano and Seto reviewed those records on which judgments had been made, and they concurred with the judgments.

**Definition of sudden death and unexplained accidental death.** We ascertained the cause of death in all deceased subjects from the death certificates. Sudden death was defined as out-of-hospital death occurring within 1 h of the onset of acute symptoms. In addition, we investigated deaths associated with accidents and extracted cases in which the accidents were liable. We defined these cases as unexplained accidental deaths, because VF might have been the cause of the accidents. Finally, we defined unexpected death as sudden death or unexplained accidental death.

**Data and statistical analysis.** Of the 4,788 subjects, we extracted those who showed a Brugada-type ECG, and we calculated prevalence at the time of the first examination, as well as the 40-year incidence, stratified according to age. The total incidence was adjusted using the 1985 world population model (8).

We showed the subjects' age at death, the interval between the onset of symptoms and death, the place of death, the cause of death and circumstances of the accidents in all unexpected death cases with a Brugada-type ECG.

To test factors contributing to unexpected death in Brugada-type ECG cases, we compared clinical characteristics, time courses of ST segment abnormalities and 12-lead ECG variables between the unexpected death group and the "other" group, which included people who died of other causes and those who were still alive. The ECG variables, including heart rate, magnitude of ST segment elevation in leads $V_1$ and $V_2$, QRS width and QT interval corrected by Bazett's formula, were measured when maximal

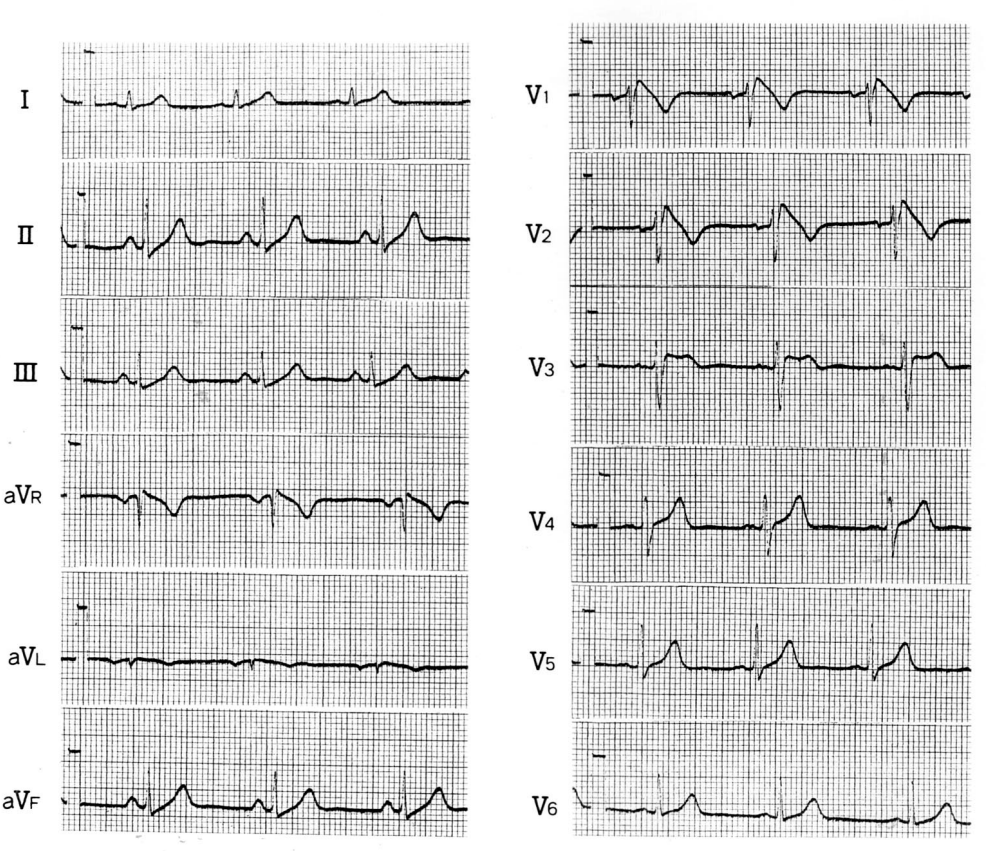


**Figure 1.** Twelve-lead electrocardiogram of a typical pattern of the Brugada type. A terminal R′ wave in lead $V_1$, a convex curve or "coved"-type ST segment elevation in leads $V_1$ (0.3 mV) and $V_2$ (0.4 mV) and "saddle-shaped"-type ST segment elevation in lead $V_3$ (0.2 mV) can be seen during sinus rhythm.

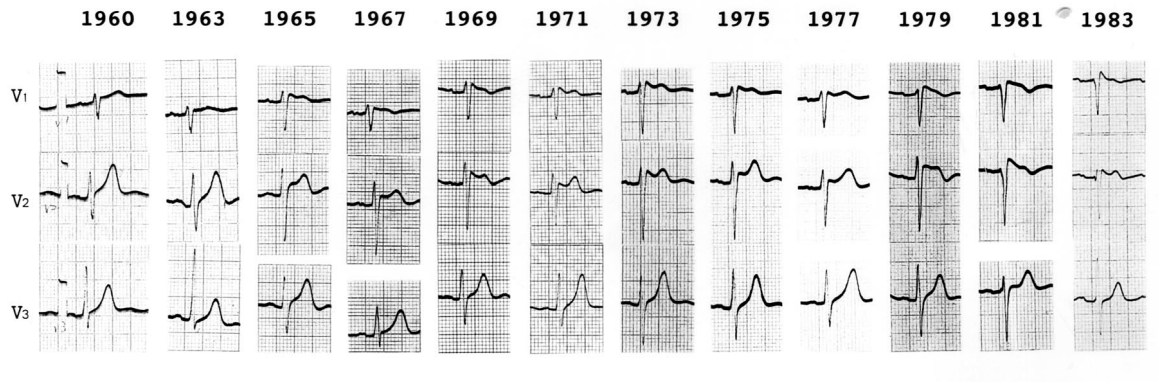


**Figure 2.** Standard electrocardiogram (ECG) leads $V_1$ to $V_3$ of a typical intermittent course taken from a subject with a Brugada-type ECG. From 1965, we observed the Brugada-type ECG with "coved"-type ST segment elevation in lead $V_1$ and "saddle-shaped"-type ST segment elevation in leads $V_2$ and $V_3$. Transient normalization was observed in 1977, but the ECG reverted to the Brugada type in 1979. Maximal ST segment elevation in leads $V_1$ to $V_3$ developed in 1981.

ST segment elevation in each case was observed during follow-up. Continuous variables are reported as the mean value ± SD and were tested using the Wilcoxon rank-sum test. Categorical data were analyzed by logistic regression analysis.

The long-term prognoses of subjects showing the Brugada-type ECG were studied. The cases were compared with the control subjects with respect to: 1) mortality from unexpected death; 2) mortality excluding unexpected death; and 3) total mortality. We used the Cox proportional hazards model to assess the difference between each pair.

Statistical Analysis System (SAS) procedures were used for analysis (9). The level of significance was set at $p < 0.05$.

## RESULTS

**Prevalence and incidence of the Brugada-type ECG.** There was a total of 32 Brugada-type ECG cases (27 men and 5 women). We could not find any evidence of structural heart disease from the physical examination, including blood pressure recordings, ECGs and chest X-rays. Although all 4,788 subjects were <50 years old in 1958, 529 were ≥50 years old at the first examination, because not all the subjects underwent the first examination at 1958. At the first examination, seven men had already presented with the Brugada-type ECG, and they were referred to as the "prevalence cases." The prevalence of the Brugada-type ECG was 146.2 in 100,000 persons. Incidence analysis was based on the remaining 25 cases (20 men and 5 women) who manifested the Brugada-type ECG during subsequent examinations. In the 25 "incidence cases," the average age at presentation was 45 ± 10.5 years. The incidence of the Brugada-type ECG was 14.2 persons per 100,000 person-years, and it was nine times higher among men than women. Of the 28 subjects for whom we could assess the time course of ST segment elevation, 25 (89%) showed an intermittent course of ST segment elevation. The rate of the frequency of the tracings showing a Brugada-type ECG pattern in the intermittent course ranged from 13% to 70% (mean 45%) during follow-up (Table 1).

**Unexpected death cases with the Brugada-type ECG.** Of the 32 subjects with a Brugada-type ECG, 5 died suddenly and 2 died of an unexplained accident. Two of the five sudden death cases (Case 2 and 4) had an episode of syncope (7 months and 15 years, respectively, before they

**Table 1.** Prevalence and Incidence of the Brugada-Type ECG from 1958 to 1999

| | First Examination (n) | | Brugada-Type ECG at First Examination (n) | | Prevalence per 100,000 Persons | | Person-Years in Incidence Study* | | Brugada-Type ECG After First Examination (n) | | Incidence per 100,000 Person-Years | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 19 | 164 | 159 | 0 | 0 | 0 | 0 | 429 | 452 | 0 | 0 | 0 | 0 |
| 20–29 | 434 | 563 | 1 | 0 | 230.4 | 0 | 2,407 | 3,173 | 1 | 0 | 41.5 | 0 |
| 30–39 | 593 | 1,244 | 2 | 0 | 337.3 | 0 | 7,099 | 11,822 | 7 | 1 | 98.6 | 8.5 |
| 40–49 | 491 | 611 | 3 | 0 | 611.0 | 0 | 9,425 | 16,764 | 6 | 2 | 63.7 | 11.9 |
| 50–59 | 203 | 195 | 1 | 0 | 429.6 | 0 | 10,535 | 17,228 | 5 | 1 | 47.5 | 5.8 |
| 60–69 | 68 | 55 | 0 | 0 | 0 | 0 | 7,570 | 12,594 | 1 | 1 | 13.2 | 7.9 |
| 70–79 | 3 | 4 | 0 | 0 | 0 | 0 | 2,799 | 4,507 | 0 | 0 | 0 | 0 |
| 80 | 0 | 1 | 0 | 0 | 0 | 0 | 519 | 731 | 0 | 0 | 0 | 0 |
| Total | 1,956 | 2,832 | 7 | 0 | 357.9 | 0 | 40,783 | 67,271 | 20 | 5 | 31.4† | 3.5† |
| | | | | | | 146.2‡ | | | | | | 14.2†‡ |

*Value of years in incidence study is the aggregate number of years contributed to each age category from 1958 to 1999 by all subjects remaining at risk for the Brugada-type electrocardiogram (ECG). †Values are adjusted using the 1985 world population model. ‡Value of prevalence or incidence for both genders of the population.

**Table 2.** Seven Cases of Unexpected Death, With a Brugada-Type Electrocardiogram

| Case No. | Gender | Age at Death (y) | Interval Between Onset of Symptoms and Death | Place of Death | Classification of Death | Cause of Death |
|---|---|---|---|---|---|---|
| 1 | M | 41 | Several minutes | Other | Sudden | Unknown |
| 2 | M | 61 | 20 min | Home | Sudden | Unknown |
| 3 | M | 63 | Several minutes | Other | Sudden | Unknown |
| 4 | F | 71 | Several minutes | Home | Sudden | Unknown |
| 5 | M | 76 | Several minutes | Home | Sudden | Unknown |
| 6 | M | 42 | 18 h | Hospital | Accidental | Rupture of the liver |
| 7 | M | 46 | 17 h | Hospital | Accidental | Cerebral contusion |

F = female; M = male.

died). Of the two unexplained accidental death cases, Case 6 drove his automobile into a parked truck and Case 7 was injured when he fell into a river just after palpitations preceding syncope. Before their deaths, none of the seven unexpected death cases had indicated any history of chest pain on effort or at rest. The average age at death in the unexpected death cases was 57.1 ± 14.2 years (Table 2).

**Factors associated with unexpected death.** The frequency of Brugada-type ECG cases with a history of syncope was significantly higher in the unexpected death group than in the "other" group. The course of ST segment elevation and ECG variables were not significantly different between the groups (Table 3).

**Prognosis of subjects showing the Brugada-type ECG.** Of the 4,788 subjects (32 with a Brugada-type ECG and 4,756 control subjects), 1,263 (16 Brugada-type ECG cases and 1,247 control subjects) were dead by the last follow-up. Twenty-seven of those deaths were classified as unexpected, 15 (5 cases and 10 control subjects) as sudden and 12 (2 cases and 10 control subjects) as unexplained accidents. Thus, Brugada-type ECG cases accounted for 26% of subjects who died unexpectedly. When age and gender were incorporated into the Cox proportional hazards model, mortality from unexpected death was significantly higher in the subjects with a Brugada-type ECG than in the control subjects. Mortality excluding unexpected death, however, was similar for both groups. Owing to the frequency of unexpected death in the Brugada-type ECG cases, total mortality was also significantly higher in the cases than in the control subjects (Table 4).

## DISCUSSION

Our population-based study of four decades revealed that the Brugada-type ECG is not a very rare condition, and subjects with a Brugada-type ECG have an increased risk of unexpected death in the adult Japanese population.

**Prevalence and incidence.** Although several studies (10–12) show the prevalence of the Brugada-type ECG, incidence data are lacking in a general population. In the present study, the prevalence and incidence of the Brugada-type ECG were 146.2 in 100,000 persons and 14.2 persons per 100,000 person-years, respectively.

Tohyou et al. (10) reported that the prevalence of the Brugada-type ECG in Japanese men was 93.8 in 100,000 persons, which is ~36% less than it was in our study population. The disparity may be due to the difference in age distribution of the subjects studied. In addition, there are no stringent diagnostic criteria for the Brugada-type

**Table 3.** Clinical Characteristics and Electrocardiographic Variables of Subjects With a Brugada-Type Electrocardiogram: Comparison Between the Unexpected Death Group and the "Other" Group

| | Unexpected Death Group (n = 7) | "Other" Group* (n = 25) | p Value |
|---|---|---|---|
| Gender (male/female) | 6/1 | 21/4 | 0.91 |
| Age at entry (yrs) | 30.2 ± 7.0 | 32.9 ± 7.5 | 0.31 |
| Age at diagnosis† (yrs) | 37.5 ± 9.3 | 47.3 ± 10.0 | 0.06 |
| Syncope (presence/absence) | 3/4 | 1/24 | 0.02 |
| Courses of ST segment elevation (persistent/intermittent)‡ | 1/5 | 2/20 | 0.61 |
| Heart rate (beats/min) | 58.3 ± 4.8 | 62.7 ± 7.4 | 0.14 |
| Magnitude of ST segment elevation (mV) | | | |
| Lead $V_1$ | 0.14 ± 0.05 | 0.15 ± 0.05 | 0.94 |
| Lead $V_2$ | 0.21 ± 0.07 | 0.23 ± 0.11 | 0.74 |
| QRS width (s) | 0.10 ± 0.01 | 0.09 ± 0.01 | 0.09 |
| Corrected QT interval ($s^{1/2}$) | 0.42 ± 0.02 | 0.41 ± 0.03 | 0.66 |

*Including individuals who died of other causes and those still alive. †Data are based on the 25 incidence cases: 6 in the unexpected death group and 19 in the "other" group. ‡Data are based on the 28 subjects for whom the time course of ST segment elevation could be assessed. Data are presented as the mean value ± SD or number of subjects.

**Table 4.** Age- and Gender-Standardized Mortality of 32 Subjects With a Brugada-Type Electrocardiogram and 4,756 Control Subjects

| | Brugada-Type ECG Cases (n) | Control Subjects (n) | Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|
| Mortality from unexpected death | 7 | 20 | 52.63 | 22.78–127.75 |
| Mortality excluding unexpected death | 9 | 1227 | 1.40 | 0.37–3.11 |
| Total mortality | 16 | 1247 | 2.17 | 1.33–3.55 |

ECG (13), which could also contribute to the difference in the prevalence data.

It is important to note that the Brugada-type ECG is a necessary, but not sufficient, criterion for the indication of the Brugada syndrome, because several other conditions, including myocardial infarction, arrhythmogenic right ventricular dysplasia and early repolarization syndrome, can cause ST segment elevation similar to that seen on the Brugada-type ECG (7). However, the coved-type ST segment elevation appeared intermittently in most of our cases, which is similar to that in patients with the Brugada syndrome (6,7,14). Furthermore, the preponderance of males and age distribution were similar to those in our Brugada-type ECG cases and Brugada syndrome patients (6,7,14).

**Prognostic value.** To the best of our knowledge, this is the first report to make an associaton between the Brugada-type ECG and its prognosis on the basis of long-term follow-up study.

Mortality from unexpected death was significantly higher in Brugada-type ECG cases than in control subjects. The age of five subjects with a Brugada-type ECG who died suddenly was relatively high, especially in two subjects who died at age 71 years (Case 4) and 76 years (Case 5). However, Case 4 had an episode of syncope 15 years before she died, suggesting that her age at the onset of symptoms may be earlier. In addition, Alings and Wilde (6) reported that the age distribution of patients with the Brugada syndrome ranged from 2 to 77 years, and their mean age at the first arrhythmic event ranged from 22 to 65 years. Unexpected deaths in this study were associated with a history of syncope among Brugada-type ECG cases. However, a history of syncope may not be useful for predicting sudden death, because more than half of the unexpected deaths occurred at the first attack. The magnitude of ST segment elevation did not distinguish the Brugada-type ECG cases with unexpected death from the "other" cases, and so it might not be useful. Although the augmentation of ST segment elevation (15,16) or specific premature ventricular contractions (17) just preceding episodes of VF have been reported, ECGs just before sudden death were not available for our study. A clustered family history of sudden death (6), response to sodium channel blockers (16,18) and genetic analysis (19) could aid diagnosis. Also, ECG recordings in the parasternal second or third intercostal space may be useful (20).

It is impossible to exclude the possibility of coronary artery disease or ruptured aortic aneurysm, without autopsy information, as causes of unexpected death in this epidemiologic study. However, our results are similar to those in the study of Omae et al. (21), who used an autopsied Japanese population in which 25% of subjects who died within 1 h of symptom onset were also classified as having "sudden unexpected death syndrome," which is now considered to be identical to the Brugada syndrome (22,23). If the Brugada-type ECG was not implicated in unexpected death, the prognosis would have been the same for Brugada-type ECG cases and control subjects. Mortality from unexpected death, however, was significantly higher in the cases than in control subjects, whereas total mortality excluding unexpected death was similar for both groups. Thus, the death certificate bias was the same for Brugada-type ECG cases and control subjects.

**Study limitations.** First, A family history of sudden death could not be incorporated in the analysis, because such data were not available from the limited information taken regarding the history of cancer and age-related disease in the family.

Second, because Brugada syndrome is believed to be a type of idiopathic VF (24), it is important to exclude structural heart disease. However, we could not perform echocardiography or cardiac catheterization in our epidemiologic study.

Third, because of the intermittent nature of the manifestation of a Brugada-type ECG, the incidence may depend on the frequency of ECG recordings. Thus, it is stressed that the present study shows results based on biennial ECG recordings. Also, the incidence in the Japanese population may be higher, because the syndrome seems to be most prevalent in Japan and Southeast Asia (13).

Finally, uncertainty about the cause of sudden or unexplained accidental death may cast a shadow on the present results, in the absence of autopsies. To solve this problem, we compared the risk of unexpected death between the Brugada-type ECG cases and control subjects, under the same conditions.

**Conclusions.** Long-term follow-up is useful for identifying the Brugada-type ECG, which was not a very rare condition in the adult Japanese population. The results of a male preponderance, age distribution (peaking around the fourth decade) and intermittent manifestation of ECG abnormalities in our Brugada-type ECG cases were consistent with the results in patients with Brugada syndrome. Because subjects with a Brugada-type ECG have an ele-

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vated risk of unexpected death, more definitive ECG criteria will be needed to screen for Brugada syndrome.

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